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Pre-Infarction Angina Elicits Greater Myocardial Viability on Reperfusion After Myocardial Infarction: A Dobutamine Stress Echocardiographic Study

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OBJECTIVES We sought to evaluate myocardial viability (inotropic reserve) after myocardial infarction (MI) and its relationship with the presence of unstable pre-infarction angina (PIA).

BACKGROUND Several studies have suggested that PIA can limit infarct size, but it is not known whether PIA can elicit myocardial viability after an acute MI, with left ventricular function improvement.

METHODS Before discharge from the hospital, 91 patients with a reperfused MI (either fibrinolysis or primary coronary angioplasty) had low-dose dobutamine echocardiography performed to assess the myocardial inotropic reserve of the infarct-related area.

RESULTS Twenty-nine patients (31.9%) had PIA in the 24-h period before the onset of MI. Nine patients were treated with primary coronary angioplasty: five (8.1%) in the group with PIA and four (13.8%) in the group without PIA. There were no other significant differences in the baseline characteristics of the patients. There were more viable segments in patients with PIA (44.9% vs. 30.7%, $p = 0.007$), and the number of patients with significant viability was higher in the PIA group (73.9% vs. 46.3%, $p = 0.026$). This occurred despite a similar number of segments with segmental wall abnormalities at baseline in both groups (46.1% vs. 46.9%, p = NS).

CONCLUSIONS The presence of previous unstable PIA induces greater myocardial viability of the infarct-related area upon reperfusion and, as such, could have considerable therapeutic and clinical implications. (J Am Coll Cardiol 2001;37:1846–50) © 2001 by the American College of Cardiology

Brief periods of myocardial ischemia before the onset of an acute myocardial infarction (MI) can delay cell death (1–3), thus preserving regional and global left ventricular function (4–6). The use of fibrinolytic therapy and primary coronary angioplasty has become widespread recently, and data on left ventricular function in this setting have been variable: some studies have indicated improved left ventricular function in patients with pre-infarction angina (PIA) (7,8), whereas others have suggested only a marginal benefit (3,9,10), and yet others have indicated that this benefit is restricted to very specific groups of patients (11–13). Recently, for example, Ishihara et al. (13) confirmed the data of Abete et al. (11) on the absence of a beneficial effect of prodromal angina in elderly patients, and, more importantly, it was found that the protective effect of prodromal angina is lost in these patients at five years of follow-up.

The present study was designed to prospectively assess the effects of the presence of unstable angina, before the onset of an acute MI, on regional and global left ventricular function and on myocardial inotropic reserve (extent of viable myocardium) in the region of the jeopardized ventricle. The objective was to identify those patients who would benefit most from this myocardial preconditioning effect.

METHODS

Patients. We selected all patients diagnosed as having had an acute MI lasting <12 h and who had been treated with either fibrinolytic drugs or primary coronary angioplasty. Myocardial infarction was diagnosed when the following criteria were fulfilled: 1) typical chest pain lasting >30 min; 2) ST segment elevation of at least 0.2 mV in at least two contiguous leads on the standard 12-lead electrocardiogram (ECG); and 3) a serum creatine kinase-MB (CK-MB) fraction concentration of more than two times the upper limit of the reference range (25 IU/liter in our laboratory) 6 to 12 h after admission. Excluded from the study were patients who had significant valvular disease, revascularization before echocardiography, post-infarction angina or infarction complicated by severe hemodynamic instability, uncontrolled hypertension, sustained ventricular tachycardia or ventricular fibrillation occurring >24 h after admission, pregnancy or a history of an adverse reaction to dobutamine,

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Abbreviations and Acronyms

CK-MB = creatine kinase-MB fraction
ECG = electrocardiogram
LDDE = low-dose dobutamine echocardiography
MI = myocardial infarction
PIA = pre-infarction angina
PIA^+ = presence of pre-infarction angina
PIA^- = absence of pre-infarction angina
WMSI = wall motion score index

or if informed consent to participate in the study was unobtainable.

On hospital admission, all patients were interviewed regarding the timing of their most recent chest pains, if any. Pre-infarction angina was defined as the presence of episodes of typical transient (<30 min) chest pain while resting, in the 24 h before the onset of infarction. None of our patients had chronic angina in the course of their normal daily life activities. We selected a period of 24 h because the beneficial effect of PIA appears to be the highest when it occurs during this period (14). Some of our patients were elderly and, as such, could be considered as suspect with respect to the subjective assessment of their symptoms. As suggested by Tombaugh and McIntyre (15) and Ives et al. (16), the cognitive status of the patient could be a confounding factor. Our group of patients appeared to be cognitive regarding their chest pain at the time of admission to the hospital, but because no specific test of dementia was applied, it is theoretically possible that some patients may have provided inappropriate information regarding their type of chest pain.

The size of MI was assessed using the area under the CK-MB curve method of Kloner et al. (1). Before the patient was discharged from the hospital, the myocardial inotropic reserve was evaluated with low-dose dobutamine echocardiography (LDDE) by a member of the investigative team who had no knowledge of the patients' group assignment. The protocol was performed according to Watada et al. (17). Briefly, during continuous ECG monitoring, a baseline echocardiogram, with the back-up of second harmonic imaging, was obtained (parasternal long- and short-axis views and apical four- and two-chamber views) and transferred to a digital station. An intravenous infusion of dobutamine was started at 5 μg/kg body weight per min and continued for 6 min. Two-dimensional echocardiography was repeated at the end of this stage, and again digitally transferred. The dose of dobutamine was then increased to 10 μg/kg per min for another 6 min, and echocardiography was repeated and digitally transferred. The transferred images were analyzed relative to the baseline images. The myocardial contractility reserve was evaluated at the 10-μg/kg dose, unless myocardial ischemia was detected on the echocardiogram, in which case, the evaluation was performed at the 5-μg/kg dose. This protocol has a high sensitivity, specificity and predictive value in detecting improvement in regional wall motion (17). The left ventricle was divided into 16 segments (18), and a semiquantitative scoring system (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) was used to analyze each echocardiogram (19). Infarct zones were defined according to the theoretic maximal risk area (18). The infarct zones of anterior, inferior, posterior or lateral infarction consisted of nine segments (apical inferior and apical lateral regions have overlapping segments). An echocardiogram was considered as technically inadequate if more than two segments could not be clearly visualized.

We performed two different analyses of myocardial contractility reserve: a segmental analysis and a patient analysis. A segment was considered to have contractility reserve if we could demonstrate an improvement of at least one grade in the scoring, excluding those segments scoring 4. A patient was considered to have significant myocardial contractility reserve in the infarct zone if an improvement in contractility occurred in at least two segments or in at least one segment when only two segments were abnormal at baseline. Those patients who had less than two segments with abnormal contraction on the baseline echocardiogram were excluded from the patient analysis, but not from the segmental analysis.

Overall and regional wall motion score indexes (WMSI) were derived from the baseline values and those obtained at the dose of dobutamine used to evaluate myocardial inotropic reserve (usually 10 μg/kg, except in one patient). The values were calculated as the sum of the segment scores divided by the number of segments scored (18).

All patients gave written, informed consent to participate, after the investigational nature of the study had been explained.

Data analysis. Continuous variables are expressed as the mean value ± SD, and categorical variables as absolute numbers of patients, with percentages in parentheses.

Statistical analyses were performed by using the chi-square or Fisher exact test for categorical variables and the *t* test for continuous variables. If the variances between the two groups were unequal (as assessed by the Levene test), the Welch correction was applied. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Originally, 130 patients were assessed in the study, 39 of whom were subsequently excluded because of post-infarction angina (n = 15), death before the scheduled echocardiogram (n = 11), revascularization before the scheduled echocardiogram (n = 10), a technically inadequate echocardiogram (n = 1) or their choice not to participate in the study (n = 2). Finally, 91 patients were assessed; 29 (31.9%) of whom had PIA (PIA^+).

Baseline characteristics. There were no differences in the baseline characteristics between the groups (Table 1), but an imbalance, albeit nonsignificant, was noted with respect to

Table 1. Baseline Characteristics of Patients With Myocardial Infarction With and Without Pre-Infarction Angina

	PIA⁻ Group (n = 62)	PIA⁺ Group (n = 29)	p Value
Age (yrs)	64 ± 12	65 ± 11	0.566
Females	7 (11.3%)	6 (20.7%)	0.232
Arterial hypertension	22 (35.5%)	5 (17.2%)	0.076
Diabetes mellitus	9 (14.5%)	4 (13.8%)	0.927
Hypercholesterolemia	25 (40.3%)	6 (20.7%)	0.066
Current smoker	27 (43.5%)	13 (44.8%)	0.909
Previous MI	6 (9.7%)	3 (10.3%)	1.000

Data are presented as the mean value ± SD or number (%) of patients.
MI = myocardial infarction; PIA⁺ = presence of pre-infarction angina; PIA⁻ = absence of pre-infarction angina.

the higher prevalence of arterial hypertension and hypercholesterolemia (35.5% vs. 17.2% and 40.3% vs. 20.7%, respectively) in the group without PIA (PIA⁻) versus the PIA⁺ group.

Characteristics and treatment of infarction. Primary coronary angioplasty was the treatment in five patients with PIA and in four patients without PIA. The extent of myocardial injury, as assessed by the area under the CK-MB curve, was lower in the PIA⁺ group (Table 2). The CK-MB time curves are depicted in Figure 1. No significant differences were observed in the pharmacologic treatment of MI in the first 24 h of infarction, except that the use of abciximab was more frequent in the PIA⁺ group (1.6% vs. 13.8%, p = 0.034).

Evaluation of myocardial viability. Dobutamine echocardiography was performed 6.4 ± 2.2 days (range 2 to 20) after the MI. This period allows for an assessment of the presence (if any) of hibernating or stunned myocardium after the infarction (i.e., viable segments with a higher probability of recovery). The number of segments assessed

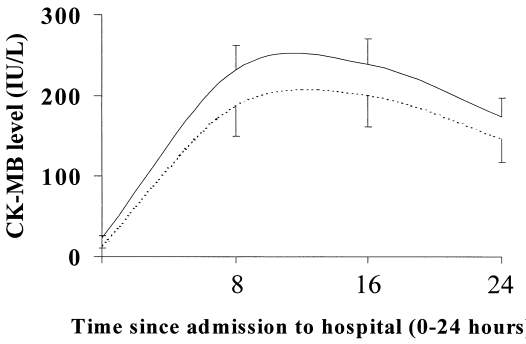

Figure 1. Time curves of creatine kinase-MB (CK-MB) in both groups. **Solid line** = patients without pre-infarction angina (PIA); **dashed line** = patients with PIA. Error bars indicate the standard deviation.

in infarct-related areas was 557 (99.8%) in the PIA⁻ group and 256 (98.1%) in the PIA⁺ group. Although the percentage of segments with wall motion abnormalities was similar in both groups (46.9% vs. 46.1%), the percentage of segments with inotropic reserve was significantly higher in the PIA⁺ group (30.7% vs. 44.9%, p = 0.007) (Table 3). Excluding those patients with less than two segments that scored 2 or 3, there were more patients with PIA who had significantly greater myocardial viability, as compared with patients without PIA (46.3% vs. 73.9%, p = 0.026). Although the WMSI values tended to be lower in PIA⁺ group than in the PIA⁻ group, the differences were not statistically different.

DISCUSSION

As shown by the increased number of viable segments, this study suggests that unstable angina preceding the onset of an acute MI can preserve regional left ventricular wall

Table 2. Characteristics and Treatment of Patients With Acute Myocardial Infarction With and Without Pre-Infarction Angina

	PIA⁻ Group (n = 62)	PIA⁺ Group (n = 29)	p Value
MI location, inferior/anterior	43/19	17/11	0.412
Delay since symptom onset (min)*	203 ± 100	219 ± 120	0.511
Primary PTCA	5 (8.1%)	4 (13.8%)	0.459
rt-PA/SK†	29/28	13/12	0.925
CK-MBmax (IU/liter)	269 ± 158	227 ± 125	0.217
MI size (U)‡	182 ± 127	140 ± 68	0.049
Oral beta-blockers	11 (17.7%)	6 (20.7%)	0.736
Intravenous beta-blockers	8 (12.9%)	3 (10.3%)	1.000
Calcium antagonists	1 (1.6%)	0	1.000
Intravenous nitrates	37 (59.7%)	17 (58.6%)	0.924
ACE inhibitors	7 (11.3%)	3 (10.3%)	1.000
Unfractionated heparin	35 (56.5%)	17 (58.6%)	0.846
Antiplatelet drugs	61 (98.4%)	29 (100)	1.000
Diuretics	8 (12.9%)	2 (6.9%)	0.493
Dobutamine	3 (4.8%)	0	0.549
Abciximab	1 (1.6%)	4 (13.8%)	0.034

*Time to administration of fibrinolysis (or "to needle"). †Excluding those treated with primary angioplasty. ‡Variances unequal (F = 6.68, p = 0.01), with Welch correction applied.
ACE = angiotensin-converting enzyme; CK-MBmax = maximal creatine kinase-MB fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase; other abbreviations as in Table 1.

Table 3. Myocardial Inotropic Reserve in Patients With and Without Pre-Infarction Angina

	PIA$^-$ Group (n = 62)	PIA$^+$ Group (n = 29)	p Value
Segments with wall motion abnormalities*	261 (46.9%)	118 (46.1%)	0.899
Segments with inotropic reserve	80 (30.7%)	53 (44.9%)	0.007
Significant myocardial viability†	25 (46.3%)	17 (73.9%)	0.026
Basal WMSI (regional)	1.81 ± 0.49	1.69 ± 0.50	0.292
Dobutamine WMSI (regional)	1.63 ± 0.55	1.44 ± 0.46	0.103
Basal WMSI (global)	1.50 ± 0.34	1.44 ± 0.36	0.405
Dobutamine WMSI (global)	1.39 ± 0.35	1.28 ± 0.30	0.135
Delta index‡	0.18 ± 0.22	0.25 ± 0.21	0.134

*With respect to the segments of the infarct zone. †Excluding those with less than two segments with wall motion abnormalities (see text for details). ‡Basal WMSI (regional) minus dobutamine WMSI (regional).
WMSI = wall motion score index; other abbreviations as in Table 1.

motion. Although the numbers of segments with wall motion abnormalities on the baseline echocardiogram were the same in patients with and without PIA, the percentage of segments that conserve their inotropic reserve (as assessed with LDDE) is significantly higher in patients with PIA. The number of patients with significant viability is also higher in this group. Hence, it is this group of patients that benefits most from PIA (i.e., patients with a reperfused MI [7,12,20] and those with episodes of PIA within a short time of the onset of infarction [14]).

Pre-infarction angina and improvement in left ventricular function. This finding could explain the post-infarction improvement in regional function observed in some studies of patients with previous angina (9,10), because it is well established that LDDE can predict the recovery of regional function (17,18,21) after a reperfused MI. Noda et al. (10), in patients with a reperfused anterior MI, observed an increase in left ventricular function (as assessed by left ventriculography) one month after infarction in patients with previous angina (48 h before infarction). Similar results were found by Nakagawa et al. (9) in patients with the same characteristics, with left ventricular function immediately after infarction similar in both groups. Ishihara et al. (7) and Liuzzo et al. (8) did not find differences in left ventricular function immediately after infarction in patients with and without PIA, but they did not analyze regional wall motion recovery, nor infarct-related myocardium viability. One recently published study (12) found better left ventricular function in patients with PIA. However, the results need to be interpreted with caution, because the study had a retrospective design in which <40% of the patients had received fibrinolytic treatment and the therapeutic dose used was inappropriate. Similar findings were reported by Anzai et al. (3), but in their study, the number of patients having ventriculography performed before discharge from the hospital was very small, and a selection bias cannot be ruled out. These investigators also reported, using multiple logistic regression analyses, that the absence of PIA was an independent predictor of re-admission to the hospital for heart failure and of cardiac mortality at one year (22). Although it is not known whether this was due to variations in left ventricular ejection fraction over the study period, it needs to be noted that patients with anterior infarctions have a lower incidence of aneurysm formation and a higher ejection fraction if they had PIA. Abete et al. (11) reported a benefit induced by PIA only in patients <65 years. Again, the study was retrospective, and data on left ventricular ejection fraction were available in <30% of the patients studied.

Influence of drug treatment. It is unlikely that the treatment given in the acute phase of MI could have influenced our findings, because all of our patients were treated either with fibrinolysis or primary angioplasty, and no clinically important differences were noted in the administration of beta-blockers or nitrates. There were more patients with PIA than without PIA who received abciximab, but because the numbers were small, the differences observed could have been due to chance alone.

Clinical implications. Our study could have important clinical implications. Low-dose dobutamine echocardiography has been used to predict recovery of dysfunctional myocardium after revascularization (23–27) or after thrombolysis (17,18,20). Those patients with PIA have a higher probability of viable myocardium in the infarct-related area, and, as such, the beneficial effect of a revascularization procedure could be higher if a flow-limiting coronary stenosis exists (25). However, it is necessary to bear in mind that segments of dysfunctional myocardium, but with signs of viability, could have less post-revascularization improvement than that predicted by contractile reserve with LDDE (25,28). On the basis of this reasoning, it is possible that the recovery of contractility of dysfunctional segments after revascularization in the present study may have been overestimated. However, not all dysfunctional segments have a flow-limiting coronary stenosis, and if viability is demonstrated, a spontaneous recovery can occur (28).

We have demonstrated that PIA can preserve viability of the left ventricular myocardium. If this mechanism could be pharmaceutically mimicked, it would be a powerful tool to conserve left ventricular function in the event of an acute MI. Indeed, a drug such as this—nicorandil—is currently available (29), and because it is a hybrid of adenosine triphosphate-sensitive channel activators and the nitrates,

its proposed mode of action would appear more efficacious, warranting further clinical evaluation.

Conclusions. Those patients who have unstable PIA and who have a reperfused myocardium (either with fibrinolysis or primary coronary angioplasty) after an acute MI have more viable myocardial segments. This finding could explain the rapid recovery of regional and global left ventricular function observed in this group of patients.

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